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## Clinical value of gastric acidity

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CLINICAL VALUE OF GASTRIC ACIDITY

Francis V. Vesely

Senior Thesis presented to the College  
of Medicine, University of Nebraska,

Omaha,

1940

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## Introduction

Why choose gastric acidity as the subject of this brief paper? There is but one reason and that is to establish in my mind a definite place for gastric analysis as a diagnostic procedure.

The analysis of a gastric content is a simple procedure and can easily be performed by the rural practitioner. It ceases to have value, however, when one does not have definite unbiased facts upon which to evaluate his results. These facts are, no doubt, unreliable in most cases, as standard text-books often reprint false statements which have become accepted as facts.

The historical background, while of little practical import, is of academic interest and has been included in order to give some idea of how difficult it is to overcome the precedence of time. Progress is slow because experimenters consider their conclusions inaccurate if they cannot verify previous results. Many erroneous facts have been published about gastric acidity and its relation to disease. An attempt to review the literature to date, and to record facts which have been proven, has been made. This paper is an attempt to correlate the facts of a positive nature and in this manner arrive at some definite conclusion as to the value of gastric analysis.

ment be tried, three pounds. van Helmont (1577-1644) and Sylvius de le Boe wrote of an acid ferment in the stomach responsible for digestion. The chemical activity alone was considered incapable of performing digestive changes, and invisible spiritual agencies known as "archaeve" were thought to govern all such physiological processes (2) (3). The work of Wharton (1656) and Steno (1661) on the salivary glands changed somewhat, for a time, the concept of digestion. Sylvius who had previously supported the theory of the supernatural, now considered the saliva as the digestive juice (2). Regnier de Graaf (1641-1673) a pupil of Sylvius de le Boe, carried out a number of experiments on the pancreas. After several attempts he finally succeeded in introducing a temporary cannula, made of the quill of a wild duck, into the pancreatic duct of a living dog, and studied the properties of the liquid obtained. He did not consider the gastric juices of any great significance and believed the pancreatic juice the next step in the process of digestion. In the latter part of the 17th century Reaumur made some important observations on the gastric juice of birds. Spallanzani, in the early part of the 18th century, collaborated Reaumur's results and established similar properties to human gastric juice.

Thus, towards the close of the seventeenth century there were various current views on digestion. It was

regarded as trituration (2) Boerhaave (1668-1783), due to action of gastric musculature, simple maceration (Haller 1708-77), and effervescence,--the view held by the chemists of the period.

While much progress was made and brilliant work was carried out by several individuals, the correlation of gastric physiology with chemistry did not begin until Prout found that the human stomach contained hydrochloric acid (1824).

It followed that since there was so much interest in the subject of digestion, some method of obtaining gastric secretions must be devised. It is possibly best to attempt to correlate the progress made in understanding digestion, with the gradual refinements as to technique of obtaining secretions from within the stomach.

1, Killing animals (2) (3). Experiments upon gastric secretion of dogs, cats, squirrels, hares, etc., were carried out by Viridet as early as 1692. These animals were killed during the fasting stage. A few years later Tiedemann and Gmelin carried out experiments using the same technique, but they attempted to stimulate gastric secretion by feeding a dog pebbles several hours before killing the animal. Condiments were also used by these early investigators, to stimulate gastric secretion during the fasting stage.

2, Reaumur (1633-1757) (1) (3) (12), repeated the

since children could swallow seeds with impunity, and suffer no ill effects, there would be little danger in the procedure.

The following are a few of his experimental procedures which gave impetus to the understanding of digestion:

He always began his experiments while fasting and always under the same circumstances. He swallowed a linen bag containing 52 grains of masticated bread. Retained the bag for 23 hours, and, upon emerging, it contained no bread, yet the linen bag was intact and still tied. He repeated the experiment, but this time swallowed two bags with equal amounts of masticated bread, but the bags were of different thicknesses. He observed that there was a fragment of bread left in the thicker bag. This fragment had lost its taste but retained its other properties.

He also swallowed meat and gristle and found that digestion took place. He found that some types of food were attacked and digested with greater rapidity than were others. It was from this work that the first conception of secretion of digestive juice arose. He believed the stimulation to secrete juice was caused by the contact of food with the gastric mucosa.

3, Vomiting was an early method of obtaining gastric juice. Reuss (1760) was the first to use this method. He found that even after the neutralization of the fast-

ing stomach that acid was present in the vomitus after a meal was eaten to stimulate secretion. He was forced to take an emetic in order to vomit three hours after taking the meal. Others such as Gosse, Young, Pinel, who were voluntary vomitors, carried on the same type of work and examined meals at various stages of digestion. There was a great degree of discrepancy in their results and therefore they proved to be of little value (2) (3).

4, Gastric fistula: It was through the accidental formation of a fistula and the fortunate presence of a man with a keen mind, that the way was paved to our present knowledge of gastric secretion and the function of that secretion. His experiments finally settled the chemical nature of the digestive process which had been discussed by Reaumur and Spallanzani during the preceding century. Beaumont (1785-1853) himself remarked of his experiments "I submit a body of facts which cannot be invalidated. My opinions may be doubted, denied, or approved, according as they conflict or agree with the opinions of each individual who may read them, but their worth will be best, by the foundation on which they rest - the incontrovertible facts".

William Beaumont became discontented with his private practice chiefly due to his friend Dr. Joseph Lovell, who was chosen Surgeon General. Beaumont was commissioned



intercostal muscles and by that means retained the orifice in the wounded stomach in contact with the external wound, and afforded a free passage out and a fair opportunity to apply dressings.

After three weeks the appetite became regular, evacuations became regular, and to all intents and purposes the gastro-intestinal tract was functioning perfectly. By spring, 1824, a valve had formed from a small fold of the stomach coat.

The experiments were begun in 1825 and continued with various interruptions to 1833. Alexis had sudden desires to wander and would leave Beaumont's residence and remain away for several years.

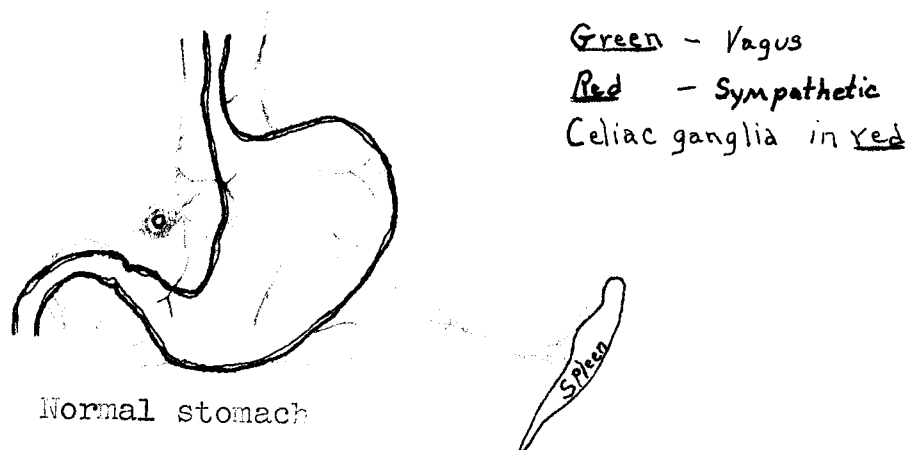
To extract gastric juice, the subject was placed on his right side, the valve depressed, and a gum-elastic tube introduced about five or six inches into the stomach. The patient was then turned on his left side until the orifice became dependent. In health, when free from food, the stomach is usually empty and well contracted. On introduction of the tube the fluid begins to flow, first by drops, then in an interrupted, sometimes in a continuous stream. Moving the tube about, up and down, or backwards and forwards, increases the discharge. The quantity of fluid usually removed was from 4 drachms, to one, and one and one-half ounces. He usually obtained the juice early

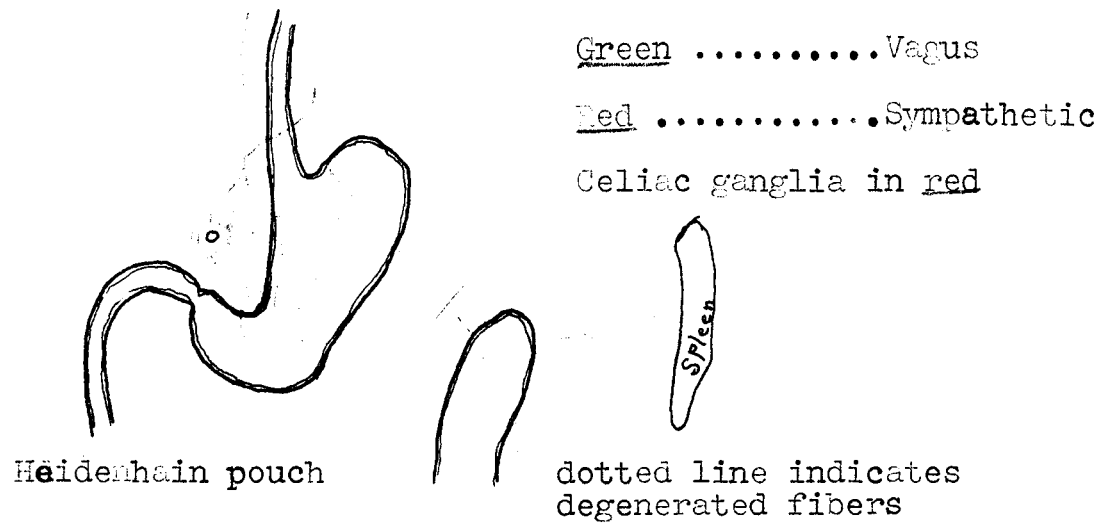
in the morning before the patient had eaten, when the stomach was clean.

Bilal could be obtained if the patient was placed horizontally on his back, by pressing the hand upon the hepatic region, agitating a little, and at the same time turning the patient to the left side.

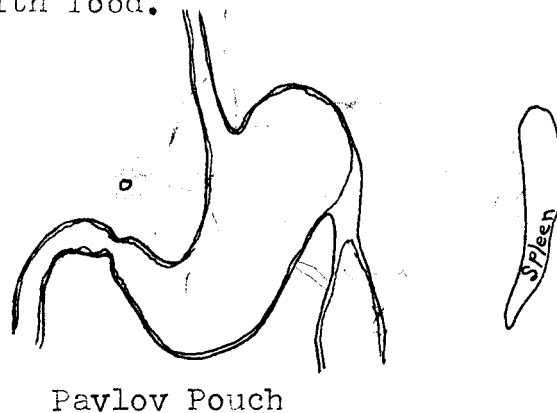
The chymous fluids were easily taken out by depressing the valve within the aperture, laying the hand over the lower part of the stomach, shaking a little and pressing upward. In this way he obtained any quantity necessary to examine and use for experimental purposes.

The accidental production of a fistula encouraged the practice of experimentally producing one. Blondlot, Bossaw, and Claude Bernard succeeded in performing this operation on dogs. Many types of operation were designed. Heiderhain and Ludwig made artificial fistulae in the dog, but they disturbed the nerve supply. Since that time many different types of pouches have been made by various investigators.





Pavlov (14) (1) (12), a student of Heiderhain, began investigations upon the physiology of the stomach when he was forty years of age. He succeeded in making a miniature stomach as a special pouch attached to the main stomach, both retaining their nerve supply. The miniature stomach opened to the outside of the body and when food was received into the main stomach the miniature pouch secreted gastric juice of the same quality as that secreted to deal with food. In this way he was the first to succeed in obtaining samples of gastric juice uncontaminated with food.



Diagrams from  
 Lim, Ivy, and  
 McCarthy (3)

5, After Human Execution: In 1848 Enderlin (2) had the opportunity of examining the gastric contents of a criminal shortly after execution. Robert Smith (15), Feb. 13, 1835, examined the gastric contents of the criminal Heidenblut. He was executed shortly after eating a meal of hard-boiled eggs, bread, butter and coffee. The examination was carried out two hours after death. Some auto-digestion of the viscus had taken place but this was inhibited to a great degree because the stomach was well filled with food.

6, Stomach Tube: Leube (2) (16) first accepted the possibility of the diagnostic value of stomach contents. In 1871 he passed the stomach tube for this purpose, for the first time. He used a stiff rubber tube, rigid like a stylet. The stomach tube is not a recent invention. Fabricius ab Aquapendente and Rumsaeus (16) in 1659 discovered what was called a stomach brush. This brush was used by beer drinkers after they had indulged excessively. The brush was used to remove excess mucus.

Boerhaave (2) first mentioned the necessity for passing a flexible tube into the stomachs of people who had taken poison, and who were unable to swallow antidotes on account of convulsions. He passed remedies into the stomach via the tube.

Hunter (16) passed flexible tubes and poured irritating substances into the stomach to cure hypochondriasis.

"His instrument consisted of a fresh eel-skin of small size, drawn over a probang and tied up at the end where it is fastened to the whale bone, and a small longitudinal slit was made into it just above this upper ligature. To the other end of the eel-skin was fixed a bladder and wooden pipe, similar to what is used in giving a clyster, only the pipe is large enough to let the end of the probang pass into the bladder without filling up the passage (2).

Physick (2) (17), an American physician (1812) used the stomach tube to neutralize an over-dose of laudanum that had been given to two brothers having whooping cough. He irrigated the stomach with epenacuanka mixed with water. He would draw out the solution and replace it with warm water. He noted an immediate improvement in his patients but later one of the boys died. The other completely recovered.

About the time this work was going on in America, Bush, Evans, Jukes and Reed simultaneously used the tube in England. They demonstrated the use of the instrument, but experiments were performed on dogs and seldom tried on human subjects.

Kussmaul in 1867 used the stomach pump for therapeutic purposes. He used it as a means of treatment for dilatation of the stomach. He noted that after repeated

are neutralized somewhat by the test meal.

The method used to-day in most laboratories is similar but the tube is passed but once. The stomach contents are not aspirated before the test begins. Samples are taken at 15 minute intervals.

The alcoholic test meal was used for some time: 50 cc. of 7% alcohol in water, was passed into the fasting stomach, and samples taken at 15 minute intervals (18) (20).

Histamine was found to be a specific for stimulation of gastric glands. It is the test that is used at present in cases of hypo-chlorhydria or achlorhydria. The amount necessary to stimulate parietal cell activity is  $\frac{1}{4}$  -  $\frac{1}{2}$  mgm. subcutaneously.

After adequate means of stimulating gastric secretion were obtained, the next problem of great interest was the study of the components of the secretion. What was the nature of the juice? Was it alkaline or acid? These problems have occupied the minds of interested men to the present date.

ed that the contents contained:

- 1, water
- 2, gelatine
- 3, muriate of ammonia
- 4, phosphate of lime

Carminati(1785) with whom Spallanzani corresponded, confirmed the foregoing results and obtained the same chemical analysis on the gastric contents of carnivorous animals. On two occasions he found that the gastric contents turned tincture of heliotrope red and completely curdled milk. He believed this action was caused by the fact that the animals had been on a diet of meat only, for a considerable period (2) (9).

Marquart in 1786 made an attempt to determine the type of acid present in gastric secretion. He examined gastric contents of cattle, sheep and calves. He found sodium chloride, calcium phosphate and ammonium chloride in all three samples. His results, as to the type of acid, were not constant and he finally concluded that the acidity of the contents was due to large amounts of lactic acid and phosphoric acid, and to traces of acetic acid (2).

After the beginning of the 19th century there was not much doubt that the gastric contents were acid, but the nature of the acid was not known. The methods of examination were crude and there was considerable difficulty obtaining accurate results. Among the acids claimed

Beaumont was not satisfied with this report and on April 2, 1833 he sent a vial of gastric contents to Benjamin Silliman, Prof. of chemistry at Yale. Prof. Silliman did not analyze the contents of the vial until August. His report to Beaumont follows:

1, Vial was kept tightly corked and the contents appeared unaltered except for formation of a pellicle upon the surface, slightly discolored by red spots. He assumed these red spots to be blood.

2, Fluid cloudy like a solution of gum arabic; clear and straw colored when filtered.

3, Odor -rather aromatic - not disagreeable.

4, Taste - faintly saline but not disagreeable.

5, Reaction - papers of litmus, alkanet and purple cabbage decidedly reddened. Turmeric paper showed no change: but when previously browned by alkalic (ammonia) the gastric juice restored the yellow color. Thus an acid reaction was indicated.

6, Nitrate of silver gave a dense white precipitate; allowed to stand in same five minutes, it turned black, indicating muriatic acid.

7, Muricates and nitrates of barytes gave a slight opalescence indicating the presence of sulphuric acid. 8, Specific gravity 1.005

Beaumont continued to send samples of gastric contents



for analysis. He sent several samples to the leading chemists of Europe, but their answers were usually delayed and when they did come the results were not accurate by their own admission (2, 9, 12).

The controversy as to the acid present was not settled until 1852. Bidder and Schmidt in Germany showed that there was an excess of chloride present over that of the bases estimated, and that the excess of chloride was alone sufficient to account for the entire acidity of the gastric juice. Even this proof was not sufficient and years later investigations again attempted to disprove the fact that gastric acidity was due to hydrochloric acid.

Up to the present time there was lacking an easy and certain test detection of hydrochloric acid. There was no need for the test until it was definitely established hydrochloric acid was the acid present in normal gastric secretion. After the work of Bidder and Schmidt, Günsburg published his test for hydrochloric acid. The test is simple and extremely sensitive. Chloroglucin is the basis of the test (2).

Alexis lived 28 years after Beaumont's death and traveled about in shows and visited medical centers for a livelihood. No conclusive experiments were performed and this valuable laboratory tool was wasted. Prof. Smith (1856) who was in the department of medicine in Penn College

All fatty foods inhibit the secretion of gastric juice and pepsin and prolong the time the food remains in the stomach. Proteins enhance the flow of pepsin. This enzyme in conjunction with the hydrochloric acid reduces native protein to albumoses and peptones. The transformation from the original protein to a soluble protein is spoken of as peptic digestion. The pepsin concentration is determined by measuring the rapidity with which insoluble protein is converted into a soluble form. The laboratory test is known as the Mett test. It consists of coagulated egg white in a tube having an internal diameter of 1-2 mm. (12) (21). Northrop (22) in 1929 succeeded in obtaining crystalline pepsin. This substance hydrolyzes gelatin, casein, egg albumin and edestin, in acid solution but is rapidly inactivated by alkalic or heat.

Gastric lipase is the fat splitting enzyme but the amount present in the stomach is very slight. The fat is only partially emulsified and then passes into the duodenum where it is acted upon by pancreatic lipase (21). Vickery and Osborne (23), 1928, studied pure gastric juice obtained from dogs, with Pavlov pouches, and found that gastric lipase did exist. They also found that it occurred in appreciable amounts in acid-free juice. The enzyme is sensitive to acid, being completely destroyed by exposure for 15 minutes, to .2 % Hcl.

Rennin causes milk to curdle very rapidly. The time

of curdling varies inversely with the concentration of rennin. The action of this enzyme stops at this point and digestion of the curd is carried on by the pepsin.

It has been shown that various foods either stimulate or retard secretion of certain functions of the gastric juice. Poly- and disaccharides do not stimulate gastric glands at all, while monosaccharides (glucose) are weak stimulants.

The hydrochloric acid is a sterilizing agent as well as a catalyst. It has been found experimentally that the principal enzyme (pepsin) of gastric juice acts at an optimum at about pH. 1.6. When an examination is made and semi-digested food is present another acid is present. This is lactic acid and is present in considerable amounts. It is produced by bacterial fermentation within the carbohydrates converting them into sugar and then lactic acid. As the contents are gradually rendered acid, the lactic acid fermentation is stopped (4, 12, 21).

The hormone probably present in the gastric juice will be discussed thoroughly later. Suffice it to say that Edkin in 1906 was the first to hypothesize the presence of internal secretion as a regulator of gastric secretion. Since his work many investigators have attacked the problem and each finds a different hormone. At present the consensus of opinion is that the hormone is histamine.

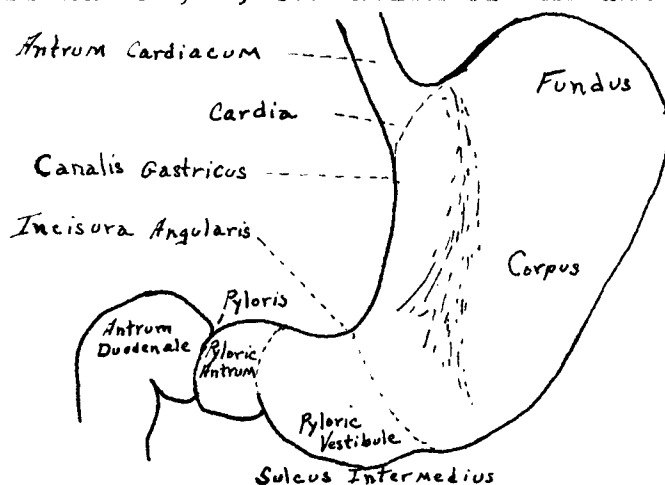
We have now arrived at an accurate analysis of gastric juice and are confronted with the problem of determining the origins of these components.

### Origin of Gastric Juice

Before confining the discussion to a review of the literature as to arrival at the present concept of the origin of gastric secretion, a brief review of the gross and microscopic anatomy of the stomach is in order.

The alimentary canal may be regarded as a tube extending the full length of the body. The stomach is the most dilated portion of the tube and is situated between the end of the esophagus and the beginning of the small intestine. It lies normally in the epigastric, umbilical, and left hypochondriac regions of the abdomen.

The length of the fully distended adult stomach is about 10". Its capacity averages about 1200 cc. The shape and position of this organ are never constant as they are dependent upon, 1, amount of stomach contents, 2, stage of digestive process, 3, development of gastric musculature, 4, condition of the intestines (3).



After F. T. Lewis  
Am. J. Anat. v.13,  
1912.

it is characterized by the presence of the pyloric glands. These zones are not rigidly set apart and there is an overlapping. Some animals present a narrow strip between the fundic and pyloric areas, which is occupied by a fourth type of glands, the intermediate (25),

The mucous membrane is lined by a single layer of tall, regular, columnar cells. The type of epithelium changes abruptly, at cardia, from the stratified squamous type. The cells on the free surface present many granules confined to the supranuclear portion of the cells. These granules consist of mucigen. After leaving the cells the granules furnish the alkaline mucus which lubricates the surface of the mucosa. Fat droplets and glycogen granules have been found in these cells but apparently the amount of glucose present in the stomach does not influence the amount of glycogen in its epithelium. Desquamation takes place and regeneration occurs from the deeper part of the foveolae where mitotic figures are numerous.

The gastric or fundic glands are the most important contributors to the secretion of gastric juice. They are single branched tubules, perpendicularly arranged to the surface of the mucosa. The glands penetrate the whole thickness of the mucosa which measures from 0.3 to 1.5 mm. The glands are straight and narrow and open through a

and pig entire gland tubules in the region of the fundus may be formed entirely of neck chief cells. In sections these cells present themselves as wedge shaped elements along the neck of the gland alternating in groups of three or more with the parietal cells, which, in this location, have a broad surface of contact with the lumen (7,8).

The cells of this type contain granular antecedents to their secretion, but the granules are so transparent that they offer little resistance to the passage of light. On sections stained only with nuclear dyes they are similar to zymogenic cells, and, therefore, were overlooked by early investigators. Their nuclei are different, however, as they are usually flat, sometimes concave, and occupy the base of the cell. In sections stained with mucicarmine or mucihematein, the cytoplasm is filled with coarse brightly stained granules, while the zymogenic cells remain colorless. This indicates that the mucous neck cells are mucus-secreting elements, but the mucus is of a peculiar kind. It differs in staining reactions from those mucus secreting cells of the gastric surface epithelium and of that of the glands of the oral cavity. Mitoses are not seen in this type of cell in the adult. It is probable that new cells arise through gradual transformation of the undifferentiated epithelium in the bottom of the foveolae. (8) (11) (25).

nection with the lumen, but where the parietal cells present a large surface there may be several of the intracellular canals communicating with the lumen. It is through this series of canals that the secretion of the parietal cells enters the lumen.

The parietal cells do not seem to undergo any morphological changes with the various stages of functional activity. In the adult the parietal cells divide, possibly by direct division, relatively often.

#### 4, Cells of Heidenhain or argentaffine cells:

This is a small cell first described by Heidenhain (1870), from the gastric glands of the rabbit. The cells occupy a parietal position on the surface of the glands. The function of the cell has not been established, although it has been ascribed both an exocrine and endocrine function. The cell stains a deep yellow when placed in bichromate solution.

The pyloric glands reach deeper into the mucous membrane and have more branches than do the gastric glands. The glands are of the simple, branched tubular type, but the lumen is larger, and the tubules are coiled so that detailed study of transverse sections is difficult. These glands contain but one type of cell. The granulations in the cells are indistinct and the cytoplasm is pale. The nucleus is usually found flattened against the base of

the cell. With some types of staining cells have been described which resemble the mucous neck cells or the glands of Brunner, of the duodenum. There is some possibility that in the human stomach the pyloric glands in the region of the sphincter, contain parietal cells.

The cardiac glands are confined to a narrow area around the orifice of the cardia. They are of a compound tubular type and resemble closely the cardiac glands of the esophagus. The terminal portions open directly into the gastric pits and show enlargements in many places. Clear glandular cells are found either alone or alternating with numerous parietal cells.

II, The submucosa is the second layer and is composed of loose connective tissue which contains fat cells, and is rich in mast cells, lymphoid wandering cells and eosinophil leukocytes. This loose layer of fibrous and elastic tissue unites the muscular and mucous coats. This layer also contains the large blood and lymph vessels and venous plexuses (8) (10).

III, The muscularis consists of three layers,- an outer longitudinal, a middle circular, and an incomplete inner oblique. The outer longitudinal layer consists of muscular fibres which are continuous with the esophagus and continue through the duodenum. They are most readily demonstrated over the lesser curvature and form a thin



ately under the epithelium.

The veins follow the same general pattern. They form a large venous plexis between the bottom of the glands and the muscularis mucosa. Another plexus is found in the submucosa but is nearer the mucosa than is the arterial plexus. The veins of the submucous plexus in the stomach are provided with valves and a relatively thick muscular coat.

Nerve Supply, The vagi and the solar plexus of the sympathetis comprise the nerve supply. The fibres penetrate the layers of the stomach and form two plexuses. The plexus of Auerbach is found between the external, longitudinal and middle circular layers of muscle. The plexus of Meissner occupies the submucous coat.

That the acid of gastric juice is a mineral acid and is present in considerable strength, is a remarkable fact that has excited much interest. Attempts have been made to ascertain the histological elements concerned in its secretion and the nature of the chemical reaction, or reactions, by which it is produced.

While Prout and Frerichs carried on extensive work along this line it was Claude Bernard(4), 1850, who first investigated the origin of Hcl using micro-chemical technique. His hypothesis of determining the origin of the acid was based on the fact that acid must necessarily be present to form prussian blue from the interaction

of lactate of iron and potassium ferrocyanide. He also believed that solutions of such salts could be introduced into the circulation, due to its alkilinity, without fear of interaction. Prussian Blue would be precipitated whenever there was contact with an acid fluid or tissue, and thereby identify the origin of the acid.

Bernard injected potassium permanganate and lactate of iron into the jugular vein of a semi-fasting rabbit. Forty-five minutes after injection the rabbit was killed and a macroscopic examination of the stomach mucosa was made. A deposit of Prussian blue was found on the surface of the mucosa, especially at the lesser curvature. Microscopic examination revealed no discoloration in gland cells or in the lumina of the glands. He concluded that the gastric glands secreted an unknown product, which, upon reaching the surface of the mucosa mixed with other fluids of the stomach and gave rise to the acid character of the juice.

That both salts had reached the tissues and were in a condition to allow interaction was proved because of the precipitation of Prussian blue if Hcl or sulphuric acid was added to the urine. Other tissues after excision, were placed in an acid bath and he found the Prussian blue reaction had taken place in the lymph glands and orifices of glands of the pharynx.

that when hydrochloric acid formed in cells, an alkaline fluid of equal concentration must also be formed which passes into lymph and blood of gastric mucosa. Thus the isolated glandular tissue should not give an acid reaction.

Heidenhain (5)(25) first recognized two types of cells in fundus glands. He also suggested a difference in action of the two types of cells. His work gave a new impulse to work being carried on as to the function of cells of the glands.

Schwald (5), 1889, believed Bernard's experiments to be valueless because iron in lactate acts as a divalent metal. Therefore the salt belongs to ferrous oxide compounds which will not form Prussian blue with potassium ferrocyanide, either with or without acid. Accordingly he used a ferric salt and carried out his work on fresh sections. Examination of the sections showed the parietal cells deep blue in color and the chief cells remained colorless. He concluded that the **parietal cells were less** alkaline than the chief cells.

Stintzing (1889) used Congo red as an indicator. He allowed the dye to run over fresh sections and examined them immediately. There were blue granules in some cells of the fundic glands. He believed this to furnish some evidence for the formation of acid in the parietal cells.

Fränkel (5), 1891, carried out a great many experiments. He did not use original methods but repeated rather completely the experiments performed earlier by Grützner and Edinger. He obtained the same results as Grützner i. e. treating sections fixed in alcohol with aqueous solution of anilin black and subsequently with bichromate of potassium, that the parietal cells became violet black in color and the chief cells dirty gray with blackish nuclei. Edinger's results were also confirmed but Fränkel objected to sodium alazarin since reaction may be brought about by acid resulting from dissociation of neutral salt. He regarded results as proving the acid reaction of gastric mucosa and the formation of the acid in the gland cells, but did not feel justified in saying this formation could be ascribed to one or another kind of cell exclusively.

A. B. Macallum (5), 1905, proved by use of silver nitrate - nitric acid method - that in comparison with the chief cells and adjacent tissues chlorides were present in abundance in the parietal cells of the gastric glands of the rabbit and guinea pig. The reaction being so pronounced as to readily demonstrate the occurrence of cells along the course of the tubule.

Fitzgerald (5) 1910, studied the source of Hcl, in the gastric secretion, in rabbits, guinea pigs and dogs. Her method was to inject the animal with a solution containing

1.5% potassium ferrocyanide and 2.25% of ammonium ferric citrate. The injections were repeated several times and either subcutaneous or intravenous , or both routes, were used. The time which elapsed from the first injection to the last varied from 3 - 30 hours. The animals were killed three-fourth of an hour to two hours after the last injection. The animals were killed by a blow over the medulla or chloroform was used. The stomach was removed and opened as early after post mortem, as possible. The mucosa was exposed and the surface examined for prussian blue reaction. The organ and contents were then placed in absolute alcohol. After the mucosa had hardened sections were cut and examined grossly and microscopically.

Examination revealed evidence of prussian blue on the surface of the gastric mucosa and in the rabbit also in the lumina of tubules and in canaliculi branching off from these into parietal cells. She noted that not all sections, or portions of a section, showed the same degree of staining. This, to her, indicated regional nature of secretory activity, and suggested the possibility that only a few gastric tubules or cells are functionally active at any one time. Certain cases showed prussian blue in situations other than those previously mentioned. No explanation was given other than there were some factors

methods, and in addition various stains, confirmed the results of Fitzgerald. Theirs were minor differences but essentially their results were the same.

Harvey and Bensley (1912) concluded that Fitzgerald's conclusions were unjustified. They used a much higher concentration of iron salts, and in addition **used** dyes, chiefly cyanamin bichloride and neutral red, which gave different colors in alkaline and acid media. They concluded that the parietal cells may form precursors of Hcl but do not produce the acid itself, the secretion of these cells giving a mildly alkaline reaction.

Ivy and Dawson (26), 1935, believe the results obtained previously are unsatisfactory because not strictly physiological methods were used. Some of their objections are:

- 1, dyes were used whose **action on the gastric mucosa was unknown and not determined** and found by them to be unsatisfactory,
- 2, Animals were previously rendered unconscious by a blow over the medulla in order to get gastric mucosa.

Ivy and Dawson found that if an animal was rendered unconscious by a severe blow on the head, the gastric secretion would stop even though the animal was secreting free acid seven minutes before stunning and 2mgm. of histamine were given subcutaneously just before the blow was delivered. There was no gastric secretion even after the second administration of histamine 25 minutes after unconsciousness began.

In abnormal people the final rise in free acid concentration was associated with low chloride value. They thought this inverted curve was due to inability to regurgitate alkalies.

Baird, Campbell and Fern (29), 1924, eliminated alkaline secretions of the duodenum by continued suction on a duodenal tube. They subjected normal individuals to the same test meal and found that they obtained identical results in both cases.

Ivy (31) 1935, came forth with the statement that gastric secretion can be divided into three phases with reference to cause:

- |                            |       |  |                         |
|----------------------------|-------|--|-------------------------|
| 1, Primary cephalic phase  | vagus | psychic-<br>reflex                         | site<br>odor<br>taste   |
| 2, Secondary gastric phase |       | chemical (antrum)<br>mechanical distention | hormone<br>secretagogue |
| 3, Intestinal phase        |       | hormone<br>reflex                          |                         |

Winkelstein (32), 1929 came to the same conclusion as Ivy, as to the mechanisms concerned in direct excitation of the gastric gland cells.

The cephalic phase is a period of adjustment. During

this period the stomach attempts to reach equilibrium both secretory and motor. This phase lasts from 30-40 minutes and it is at this time that impulses are transmitted from the central nervous system to the gastric glands along the vagi.

Pavlov (14) was the first to demonstrate experimentally the fact that secretion of gastric juice is under the control of nervous fibers. He found that section of the vagi abolished the effect of sham feeding.

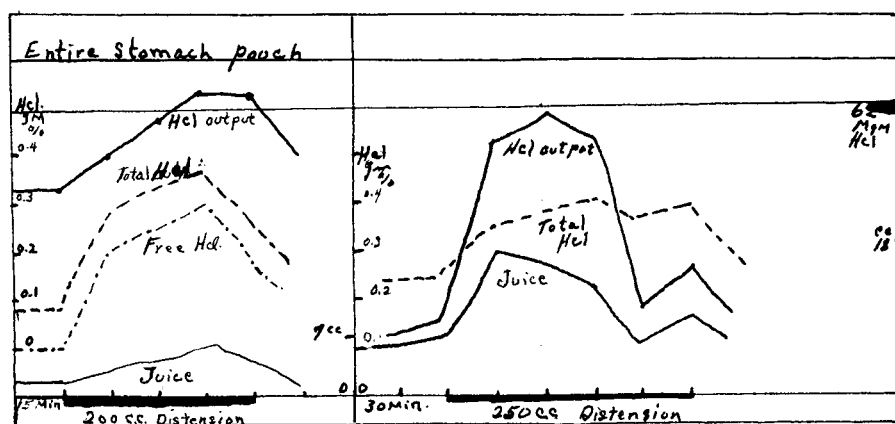
Reflex stimulation of vagi through the sensory nerves of the buccal cavity, or through other organs, as well as artificial stimulation applied directly to these nerves by means of an induction current elicits a copious flow of strongly acid gastric juice rich in pepsin and "dissolved mucin". Sham feeding produces a large amount of "visible mucin" especially at the end of the secretory period, or during secretion, produced by application of a weak induction current to the vagi. This type of secretion may be arrested by atropine and is not affected by ergotomine. The source of visible mucus "is probably the surface epithelium of the fundic mucosa. The fact that gastric glands produce a "vagal type" of secretion in response to acetylcholine or choline and that gastric secretory nerves may be paralyzed by small doses of atropine suggests that the chemical transmitter of vagal



secretory impulses is acetylcholine. Therefore the vagus may be regarded as a secretory nerve for the peptic and parietal cells of the gastric glands, as well as for the surface epithelial cells of the gastric mucosa.

The secondary gastric phase is characterized by mechanical and chemical stimuli in the stomach. This is the period that the secretory and motor function are at their height. This period lasts from 1 hr. to  $1\frac{1}{2}$  hours, and probably represents the highest period of dissociated free Hcl, and therefore, from a chemical standpoint is the most effective in gastric digestion.

Sim, Ivy and McCarthy found that distention of the stomach with a bag stimulated gastric secretion. They also believed that motility of the stomach was involved in some way. They found that gastric secretion, caused by mechanical distention, was inhibited by hypodermic administration of 1 mgm. atropin or by the introduction of fats into the stomach. The following is a table illustrating the effect of distention on gastric secretion:



Diag. from (2)

intravenously, caused a drop in the blood pressure and also inhibited the pressor action of epinephrin and pituitrin. Chemical analysis proved this substance to be Iminazolyloethylamin (histamine) an amine derived from amino acid histidin, a cleavage product of proteins. The production of histimine was believed to be due to decarboxylation of the amisCacid by bacterial action.

Physiological reactions observed by them on human beings, were:

- 1, Histamine subcutaneously produces a flow of gastric secretion.
- 2, Subcutaneous injection of 1cc. of 1:1000 is harmless.
- 3, Histamine is of value in differentiating true and pseudo achylia.

McCann (29), 1929, performed a series of investigations upon dogs, having complete resection of the pyloric antrum. He found that after injection of histamine there was no change in the three variable factors (increase in rate of secretion, change from a mucoid to a watery clear secretion, and an inverse fall in the curve of neutral chlorides) as observed when injections were made into normal dogs or into dogs with only a partial resection of pyloric antrum. While he did not attempt to isolate an active principle he did prove that the prepyloric segment was essential for secretory response in the dog.

. Sacks, Ivy, Burgess and Vandolah (38), 1938, isolated histamine as a sulphate from the pyloric mucosa of a hog which precludes the possibility that it is present as a result of putrefactive changes. There is some experimental evidence that histamine is the hypothetical hormone gastrin which was first described by Edkin.

Toby (40), 1936, demonstrated that the chloride concentration of gastric juice secreted in response to histamine administration was of the same order as the chloride concentration of the juice obtained reflexly through vagal stimulation. This points to a close similarity, of not identity, of Hcl formation in both cases.

McIntosh (40), 1938, from the work of Toby, formulated a hypothesis that histamine is liberated within or near the parietal cells as a result of vagal stimulation and that histamine thus liberated is responsible for the secretory activity of the cells.

He supports his hypothesis by the following laboratory data. 1, The histamine equivalent of gastric juice obtained by vagal action is much higher than that of the plasma therefore the mucosa must be the source of the histamine. 2, Histamine equivalent of histamine juice, is about the same as that of "vagus juice".

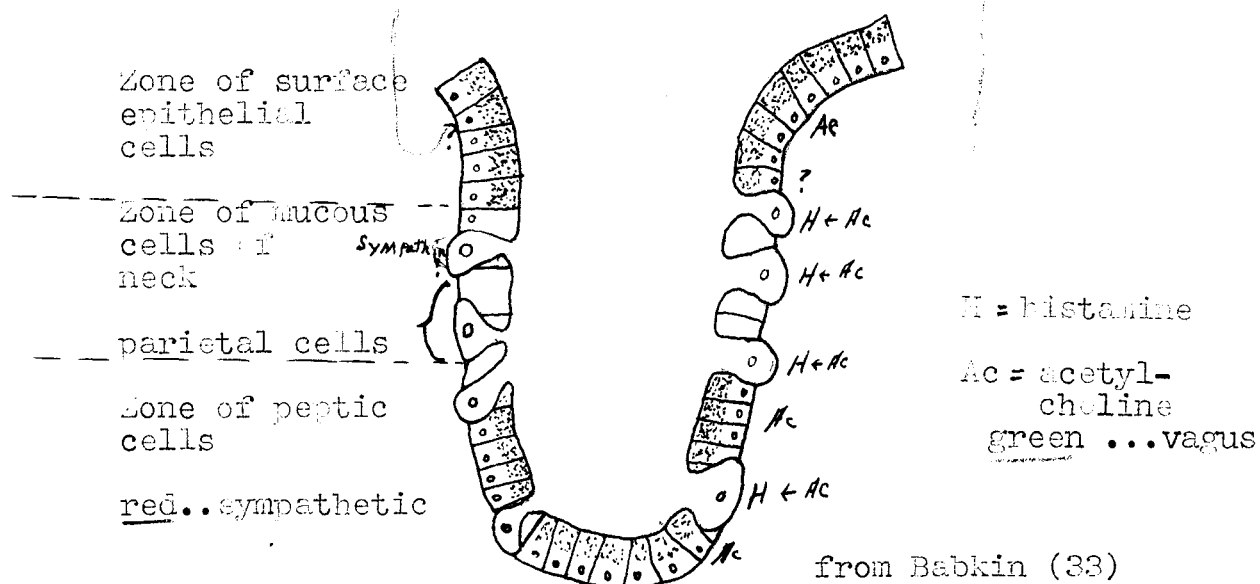
3, Tendency for high equivalent of "vagus juice" to be associated with rapid secretion.

Further evidence which points to the above hypothesis may be drawn from Babkin's work on the secretory mechanism of gastric glands (33).

Gastric glands produce a "vagal" type of secretion in response to acetylcholine or choline, and the glandular secretory nerves may be paralyzed by small doses of atropine. These facts suggest that the chemical transmitter of vagal secretory impulses is acetylcholine.

Histamine stimulates parietal cells almost exclusively, as shown by Babkin and Vineberg, Webster, Cowgill, and Bowie, affecting the mucous and peptic cells hardly at all. In certain doses it inhibits the activity of the last two types of cells. It has also been shown that histamine inhibits action of vagi on peptic cells, preventing discharge of zymogen granules (27, 33, 41).

Since the histamine equivalent of gastric juice is higher than that of the plasma and histamine is the strongest stimulant of parietal cells, and since the histamine equivalent of "vagal" and "histamine" gastric juice is the same, it is probable that histamine is conveyed into the gastric juice in conjunction with the secretion of the acid producing cells. From the facts stated it may be concluded that the action of the vagus on gastric glands causes liberation of histamine, or histamine-like substance, which stimulates parietal cells.



That histamine is present in gastric juice at all times in a free state has not been definitely established but Babkin (33) has some evidence to uphold this belief. The following is a brief summary of his experiment:

Samples of gastric juice were obtained by sham feeding, subcutaneous injection of histamine in dogs with esophagotomy and gastric fistula, as well as under vagal stimulus. All samples contained a substance that acted like histamine on guinea pig ileum. The substance proved to be histamine.

Whether histamine in the hormone concerned in the second (pyloric, gastric) phase of digestion has been neither proved nor disproved. The majority of investigators have a tendency to uphold the affirmative.

Other hormones or secretagogues have definite effects on gastric secretion and the one receiving the most atten-

tion and rivaling histamine as the substance in the second phase of digestion is gastrin.

Activating substances which earlier investigators called gastrin have been discussed sufficiently, and only recent works will be considered.

Kornsaw (42), 1938, isolated a preparation from the pyloric mucosa which, when injected intravenously, elicited a gastric secretion with high acidity and low pepsin contents. This result was obtained on cats. The preparation did not exhibit histamine or choline like depressor activity and had no effect on pancreatic secretion. He concluded that the pyloric mucosa contains a specific hormone (gastrin) which excites gastric secretion.

Gray, Wiezorowski, and Ivy (43), 1939, obtained a substance from hog- and dog-mucosa which was devoid of vaso-depressor substance but toxic to affecting motor and respiratory centers of brain. The substance was not present in fundic mucosa nor in liver. The preparation elicited a gastric secretion characterized by high acidity and low pepsin content, on intravenous or intramuscular injection, and was termed gastrin.

Other secretions which are known to effect gastric secretion are: 1, Enterogastrone which has a depressing effect upon gastric secretion was first extracted from duodenal mucosa. A substance was isolated by Gray, Wiezorowski and Ivy (44), 1939 from human male urine which

had the following characteristics: The active principle was stable to five minutes boiling, it had no effect on gastric motility and was free of vaso-dilator action and no gonadotropic activity. This substance may be identical to enterogastrone.

Culmer, Atkinson, Ivy (44), 1939, found that pregnant urine contained a substance which inhibited the volume of free acid and total acid present in gastric contents. The experiments were performed on dogs which received A. P. L. doses of 1000-5000 rat units daily for five consecutive days.

The substance present in human pregnant urine having the above effect is probably not A,P.L. sex hormone. The A.P.L. sex hormone is damaged by heating to 60° C. and completely destroyed by boiling. The substance which is present in pregnant urine depresses gastric secretion is not an A.P.L. substance.

Some other important factors which normally enter into the regulation of gastric acidity are: 1, rate of secretion, 2, motility, 3, osmotic relationship of blood and gastric juice.

1, The composition of gastric secretion as related to the rate of secretion.

a, The output of free Hcl, Chloride, neutral chloride, and potassium, bear a direct relationship to volume and rate of secretion of gastric juice. The output of

calcium and sodium is constant.

b, The concentration of free Hcl and chloride bear a distinct relationship to the volume rate of secretion. The concentration of potassium remains constant at 7 milli equivalents per liter.

c, The concentration of Hcl bears an inverse linear relationship to the concentration of neutral chloride.

d, The factor of neutralization by mucus has little import as shown in the table (27, 28, 45).

Time min.	Descri tion	pH	Volume cc.	Milliequivalents per liter		
				Free Hcl	Total chlor ides as cl	Base
Fast ing	Mucus	1.7	1	78	125	47
30'	Mucus++	1.5	2	98	140	44
60'	Mucus++	1.4	2	121	158	40
90'	Neg.	1.5	4	89	125	35

2, The motility of the stomach is variable and we find that normals may fall into either the hypomotile group or the hypermotile group. It is generally considered that a rapid emptying of stomach contents means low acidity (45, 46, 47).

3, The relationship of blood electrolytes to gastric chlorides has been a controversial question. At present it is believed that there is a definite osmotic relationship between the blood and gastric juice



and also between the osmotic pressure of gastric juice and total chloride content of the gastric juice.

a, Total chlorides may be secreted in concentration equal to the total electrolytic concentration of blood serum.

b, Parietal cells may secrete chloride at a concentration equal to, or below, the total electrolytic strength.

c, Free Hcl is never equal to the total electrolytic strength but it may approach it.

d, The total chloride concentration of the gastric juice limits the maximum acidity which this fluid can attain.

e, The osmotic pressure and chloride concentration of gastric juice is regulated by osmotic pressure of the blood. The fundamental mechanism involved is the water exchange through a membrane impermeable to the chloride ion.

f, The Relationship between osmotic pressure of blood and rate of secretion of gastric juice is inversely proportional to osmotic pressure of the blood. This is explained on the basis of change in the permeability of the capillary bed produced by marked physical changes in the circulating fluid (27, 46, 33, 48, 49, 50).

### Gastric Acidity in Disease

Before beginning a discussion of acidity associated with pathology it is necessary to have some conception of the normal response to food.

It is difficult to establish a normal curve as each individual has a more or less characteristic response which is normal for him. The normal response can roughly be divided into three curves depending upon the rapidity of reaction to a given stimulus, height of curve, and descent of the curve.

Bennet and Ryle (30) 1921, selected one hundred healthy medical students and made gastric analysis by the fractional method and formed three types of curves. These types were designated as hyposecretory, isosecretory, or hypersecretory, depending on their respective reaction to a stimulus.

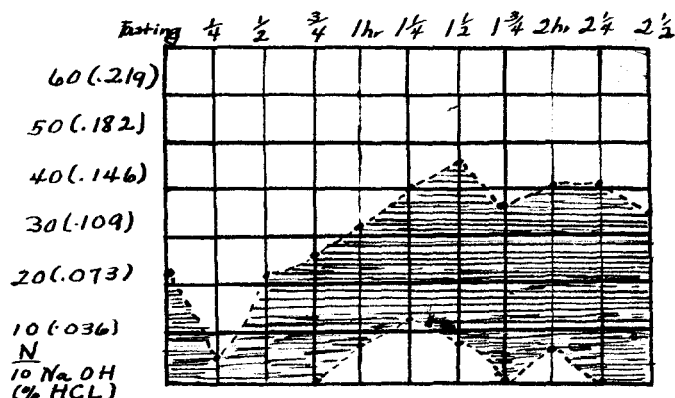
They termed the response an isosecretory type if there was a steady increase of free Hcl from 5 to 40% N/10 NaOH at the end of one hour with a subsequent steady fall to the original level. The entire process occupying about two hours.

The hypersecretory type is characterized by a rapid rise in Hcl to 70 or more, which high point is maintained with little if any decline. The food left the stomach in the normal time which is 2 -  $2\frac{1}{2}$  hours, but even after this

had taken place, gastric juice continued to be secreted. The curve of total acidity runs a parallel course about 10 points above free Hcl.

The hyposecretory curve is similar to the isosecretory but with slower ascent. The high point was from 40 - 50% N/10 NaOH.

From their studies they compiled a standard chart designating the limits of free Hcl in 80% of normal people after a gruel meal.

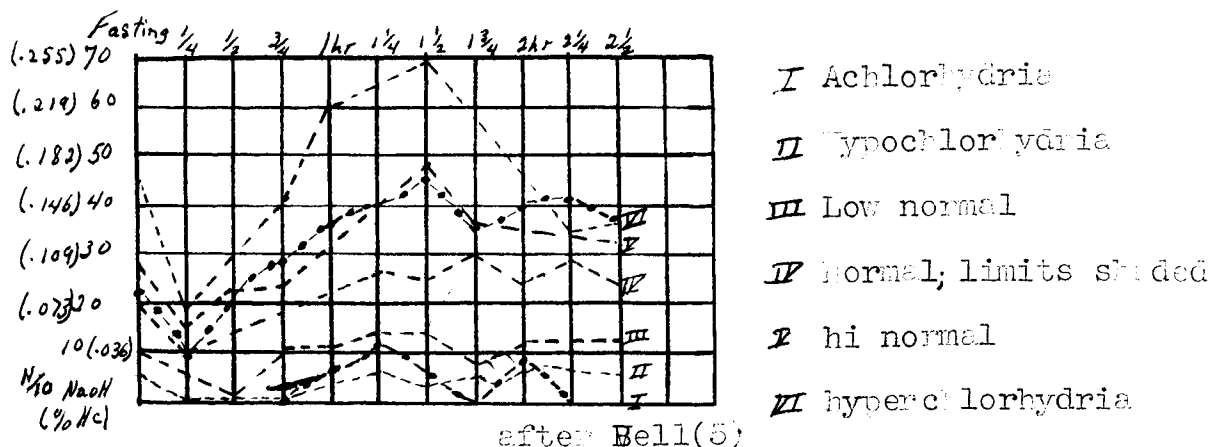


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Bell(5) 1922, performed a series of 425 gastric analyses by the fractional method. From his studies he constructed a chart and found that 80% of people stay within the outer limits of the normal zone. He suggested six types of curves, of which only three, achlorhydria, hypochlorhydria, and hyperchlorhydria, were outside the normal range.

He divided his normal zone into the following three

types: low normal, normal, and high normal.



A great deal of emphasis is placed on acidity in disease, but very few workers have noted the normal changes in acidity with respect to age.

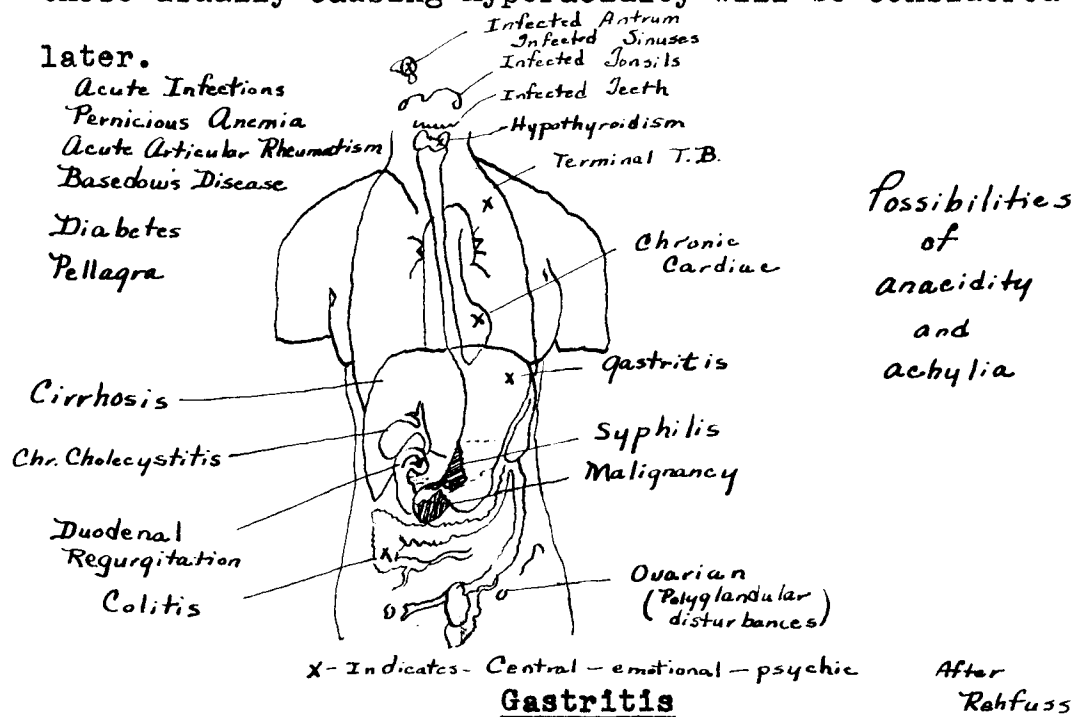
Bell (51) 1922, made examinations on 100 people and found that there was a decline in gastric acidity with increasing age. Keefer and bloomfield (52), 1926, made similar observations and came to the same conclusions.

Vanzant, Alvarez, and their co-workers (53), 1932, studied the range of acid in 3746 cases at various ages. They found that the free gastric acidity rose rapidly from childhood to 20 years of age, and that about puberty the gastric acidity of males surpassed that of females.

Ruffin and Dick (54), 1939, say that, decade for decade, the mean for gastric acidity for women is found lower than for men.

It is evident from the variation found in normal

individuals that the problem of attaching pathological significance to gastric acidity is indeed a great one. It is for this reason that only the most common disorders of the stomach will be considered in some detail. Those diseases which are usually associated with hypochlorhydria or achlorhydria will be considered first and those usually causing hyperacidity will be considered later.



This was a diagnosis made often, a few years ago. It was the name attached to any dyspeptic condition. The diagnosis is again being made both with more certainty than previously, due to the gastroscope.

The etiology of this disorder is not known but it is certain that there are some factors which make parti-

cular individuals prone to develop this type of disease entity.

Individuals with a low acidity are likely to develop this condition. Other factors which cause it are systemic diseases, acute infections, and anemia.

The pathological picture is well understood since gastroscopic examinations are being done. There are two types, the atrophic and hypertrophic.

The hypertrophic type presents a dark red, mammillation of the mucous membrane. The rugae are more pronounced and tortuous than normal. Usually this type of gastritis is associated with hyperchlorhydria (55).

The atrophic type of gastritis is more common than the hypertrophic. It is always associated with hypochlorhydria or achlorhydria, and an increase in mucus (55, 46, 33).

The pathological picture is one of atrophy. The mucous membrane is thin and pale. The mucosal folds are easily obliterated on air inflation. The mucosa is very thin and often areas of erosion can be seen during the gastroscopic examination. One of the most common complications is severe hemorrhage. This type of mucosal atrophy is often associated with pernicious anemia, gastric carcinoma, gastric syphilis, and anemias (56, 46, 33).

### Pernicious Anemia

This condition has been recognized for many years and has caused a great amount of speculation as to etiology and whether the disorder of the stomach precedes and is the cause of pernicious anemia, or whether it is secondary to the disease.

Fenwick (57) 1877, first recognized diminished secretion in pernicious anemia and was also the first to correlate gastric atrophy with the disorder. He believed that the atrophy was the primary source of trouble. His opinion went unchallenged for many years.

Hurst (58), 1922 believed the cause of the atrophy was a haemolytic toxin produced by some infection in the alimentary canal.

About the year 1900 there were men who expressed the belief that gastric changes were secondary. It was not until Castle (59) came forth (1929) with his idea of "conditioned" defect of mutation that much progress to understand the disease was made.

Castle said that the patient was unable to derive from his food some substance essential for normal function of bone marrow. There was a failure of reaction between a substance in food (extrinsic factor) and a substance in normal gastric secretion (intrinsic factor).

His views are expressed by the formula:

F x G		F	food (extrinsic)	G (gastric or
	L.E			intrinsic)
I		I	intestinal permeability or	

any defect causing malabsorption, or destruction of those substances, or a product of their ineffective interaction.

~~L.E.~~ fever extract - thermostable factor in mammalian lives, kidney and other organs.

Factors which must be considered as predisposing an individual are: 1, Does age wear out the mucous membrane? It has been proven that there is a decrease in acidity with increasing age.

2, Constitutional types may secondarily have a bearing on the disease.

Pathology as revealed by the gastroscope examination shows a different atrophy of mucous membrane of the body of the stomach. The mucous membrane shows atrophic changes and is thin and pale. The degree of thinness is judged by the height and thinness of the mucosal folds and the ease of their obliteration on air inflation. This atrophy usually extends over the entire surface. A characteristic feature is the presence of branching submucous vessels which impart a bluish network to the pale, thin background.

Gastric analysis reveals a characteristic curve. There is an achlor~~hydria~~ after a test meal and only very seldom is any acid found even after histamine has been



injected. Pernicious anemia has the most constant acid curve of all pathological processes.

Morrison (61) 1933, believes that Neutral red is superior to histamine in testing the gastric mucous membrane for latent secretory and excretory powers which are occasionally present in pernicious anemia. Pepsin is usually absent.

The diagnosis of pernicious anemia should seldom be made in the absence of achylia gastrica. Achylia occurs in 99% of the cases.

The prognosis of this disease cannot be determined readily. It depends upon the extent of the disease, and upon proper treatment instituted immediately. The only time one can give a definite prognosis is after the case has been treated for some time.

#### Macrocytic anemias

These are considered here because of their close relationship to pernicious anemia. In some cases of non-Tropical Sprue (Geis disease, idiopathic Steatorrhea) this type of anemia develops.

Some cases are thought to be due to lack of either the intrinsic or extrinsic factor.

Early investigators thought this disease to be associated with achlorhydria in about 50% of cases(62).

Later the incidence of achlorhydria was reduced to about 15% according to results obtained by Bennet, Nunter and Vaughn (63), 1933. They report twelve cases and two of these had achlorhydria.

The results of the above investigators cannot be evaluated as they do not give their procedure. No note is made whether or not they used histamine. Smeel, Camp and Watkins report 15 cases. They found free Hcl with histamine stimulation (64).

Like pernicious anemia, these cases respond to liver extract.

Other conditions which occasionally develop macrocytic type of anemia are anemia of pregnancy and people infected with fish tapeworms.

### Syphilis

Syphilis of the stomach used to be regarded as a rare condition. Recently a fair number of cases have been reported but it is difficult to prove, conclusively before autopsy that a syphilitic condition is present. The development of the Wassermann reaction, roentgen-ray diagnosis, and gastroscope have made early diagnosis more conclusive but not infallible.

Pathology of gastric syphilis as described by Levitt and Castiglia (65), 1939, upon gastroscopic examination reveals a stomach that is short and lying high. The

pylorus was not visualized. The entire stomach, including the antrum, showed a rather marked rigidity. The wall was thick, granular and red.

Roen and Thorner (66) 1939, and Eusterman (67) 1931, describe the usual lesion found as a gumma which will eventually ulcerate. They describe the mucous membrane as having the appearance of a typical diffuse chronic atrophic gastritis.

The cases may be arranged, according to clinical symptoms, into three groups.

- 1, The early infection simulates symptoms of gastric ulcer. The gastric acidity at this time is normal or above normal. This is not the stage that visits the physician.

- 2, The second stage of progress of the infection presents symptoms resembling those of carcinoma. The patient at this stage is the one seeking medical attention. At this time there will be either a low concentration or an absence of free Hcl. This lack of acidity may be the precursor of the diffuse gastritis which develops at a latter stage. The acid returns in these patients after adequate treatment.

- 3, The third clinical group presents atypical cases. At this stage of progress the inspection may simulate any disease entity. A chlorhydria usually found at

this time.

	cases.	Hyper.	Normal	Hypo.	Achl.
Hurst	2	0	0	2	0
Levitt	1	0	0	0	1
Euster- mann	93	0	0	0	93

Syphilis is a common infection but only 4% ofluetics complain of gastric symptoms. Of this number 87% gave stomach trouble as their chief complaint (66). On observations based on 93 patients it was found that 70% of the number were men and 28% were women. The average age of the women was 36  $\frac{1}{3}$  and of the men 39  $\frac{1}{3}$ , One half of the total number of patients were in the third decade of life. Serology was positive in 92% of cases (67).

While there is specific treatment for the infection it should be diagnosed long before this stage (gastric) of syphilis is reached. This is true since a very few gastro-intestinal tract.

#### Gastric Carcinoma

Cancer is the most talked of pathological entity affecting the human race. That it is a great problem about which our knowledge is limited, is shown by the fact that in 1935 there was a total of 1,392,052 deaths and 137,649 were due to cancer. Of the number due to cancer, 66,461, or about 48%, were due to carcinoma of the digestive tract

and peritoneum, Cancer of the stomach accounted for 46.2% of this last group (68).

This is not a modern disease as the Greeks made reference to it in their writings. Galen attributed cancer to black bile. He had little faith in the corrosive pastes used by the Egyptians, and Celsus advocated cauterization. He recognized that chemical irritation aggravated the disease. The Galenic school held sway for 1000 years.

Johannes Muller published the first histological description of diseased tissue in which the cellular structure was clearly described. Hanan, 1889, succeeded in transmitting animal tumor. His work formed the basis of experimental cancer (69).

### 1, Etiology

Many theories as to pathogenesis of cancer have been postulated since the time of Galen.

Fibiger, 1913, produced cancer of the stomach in rats, by introducing animal parasites.

Virchow believed that malignancy was caused by chronic irritation. Chemical theories have also been advocated. Since the work of Maud Slye the geneticists have advanced theories as to the formation of new growths on a hereditary basis.

Another exciting factor is heat. Constant burning

or overheating produces a stimulus which causes the tissue to hypertrophy. This hypertrophy is on a protective basis and later may undergo malignant degeneration.

Gye and Bernard (80), 1925, performed some carefully controlled experiments as to a possible cause of cancer. The following is a record of their findings.

- 1, All malignant new growths contain an ultra-microscopic virus or group of viruses, which can be cultivated. The virus probably resides within cells of the neoplasm.

- 2, Virus alone, washed free from all adherent material, does not produce a tumor when irrigated, and does not produce a visible lesion.

- 3, Injected animal with virus free extract of tumors, the virus produces a malignant new growth, "Specific factor".

- 4, There is no specie in so far as the virus is concerned, for tumors can be obtained in one specie of animals with the virus obtained from the tumors of another.

- 5, Specific factor shows a strict specificity of species, thus, in order to produce a malignant new growth in a mouse, it is necessary to use the specific factor from a mouse tumor.

- 6, There is probably also a strict specificity of tissue for the specific factor for carcinoma, reproduce

carcinoma and not sarcoma.

Factors which predispose an individual to cancer are:

- 1, Age,-the incidence increases with age.
- 2, Heredity,-proven by Maude Slye on her mice.
- 3, Sex,-The ratio of men to women afflicted, is 3:1
- 4, Trauma,-Continued irritation is the more usual factor, but severe trauma may produce malignant changes.
- 5, Conjugal condition,-Cancer spreads by body fluids or by transplants, but not by mere apposition.

#### Pathology

Site and morphology are two factors which influence the the pathological process. Statistically carcinoma of the stomach may be divided as to location or site.

1, Carcinoma of the pyloric region and lesser curvature and become stenotic by encircling the pyloric aperture. One-half of all carcinoma of the stomach is of this type. 2, Carcinoma of the body along greater or lesser curvature or on anterior or posterior wall. Usually the growths originate on the lesser curvature.

3, Carcinoma of cardiac end occurs in about 8% of cases. 4, Fundus or dome is involved in about 1.4% of cases. 5, Diffuse schirrhous type which involves the entire stomach is found in about .8% of cases (68, 70, 71).

There are four types of carcinoma which may occur in the stomach, namely, medullary carcinoma, scirrhous carci-

noma, adenocarcinoma and colloid carcinoma.

Morphologically Ewing recognizes two main gross types of carcinoma.

1, The first type is a soft more or less circumscribed tumor in the cardia or fundus. These tumors reach a considerable size. They are a very vascular tumor and produce disturbances in rate and manner of emptying of the stomach. The emptying time is shortened under two conditions. a, Infiltration of the pyloric region paralyzes the pyloric musculature and converts the pyloric canal into a rigid tube. The meal passes directly through the stomach and fills the duodenum.

b, Usually in achylia because there is a disturbance of normal pyloric reflex.

The emptying time is prolonged in pyloric stenosis and may be combined with dilatation of the stomach (46) (70), (71).

The presence of achlorhydria in the majority of cases of carcinoma of the stomach has been observed since the earliest days of gastric analysis. It was formerly the belief that achlorhydria was an effect of the carcinoma, produced either directly by destruction of the acid secreting mucous membrane, or indirectly by the gastritis to which it gives rise. The present belief is that the achlorhydria precedes the onset of the carcinoma and is



itself an expression of the previously existing gastritis which in turn has rendered the mucous membrane prone to malignant change.

Achlorhydria may be a physiological change in the later decades of life. It was shown that acidity decreases with age and Hartfell on gastroscopic examination finds atrophic changes along with superficial changes in 60%. That carcinoma does not cause achlorhydria is evident when one considers that when carcinoma occurs in an individual in whom hyperchlorhydria is present, the hyperchlorhydria persists unchanged in spite of progress of the disease. Some believe this to be evidence that carcinoma can arise on a previously existing ulcer (56, 68, 71).

#### Composition of Gastric Juice in Cancer.

1, Sub-acidity in from 70% - 80%. This is not an early sign generally. Tumors in the pyloric region give early symptoms and hence chemical examination is performed early and accounts for the normal acidity or hyperacidity.

2, Large amounts of blood and coffee-ground material are of significance.

3, Mucus is found in greater quantity and there is more cellular material than in chronic gastritis.

4, Greater amounts of solid albumin are present.

5, Blood, pus, muco-pus, and increase in albumen content are indicative of an advanced ulcerating carci-

noma.

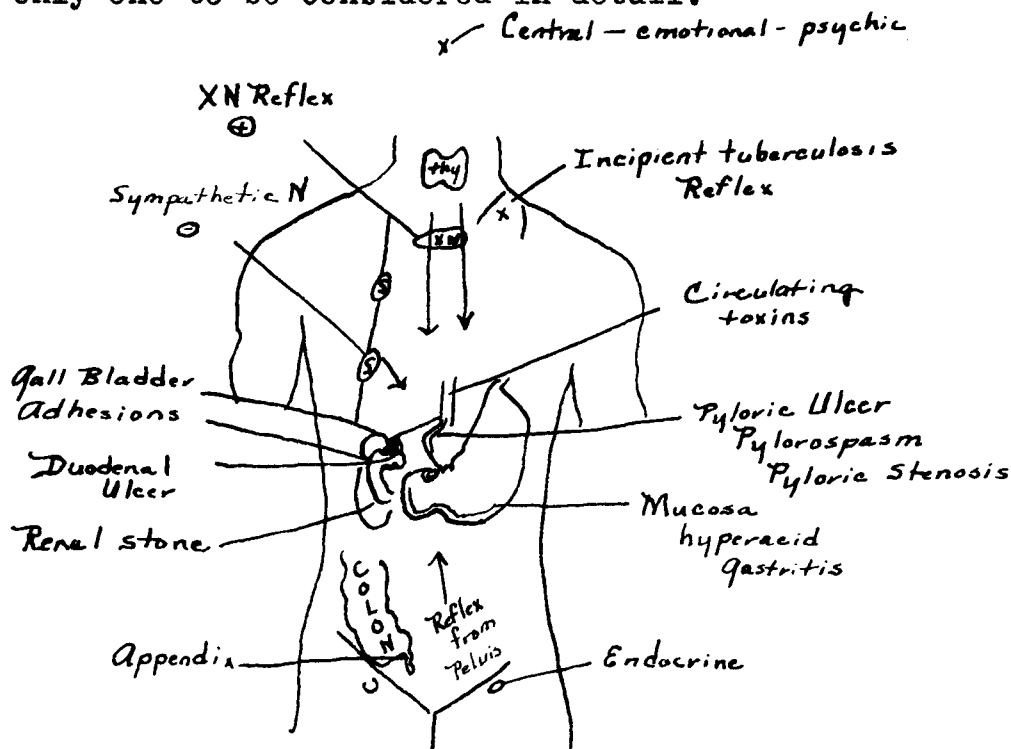
6, Lactic acid is usually found in carcinoma but it may also be found in the presence of stenosis.

7, The protein nitrogen and non-protein nitrogen partition of the gastric juice is much higher in carcinoma than in normal.

8, Pepsin is usually absent especially in large infiltrating tumors (72, 71, 68, 27, 33, 46, 47).

9, Zoeppitz estimates the frequency of symptoms as follows: occult blood 94.5%; anacidity 88.9%; lactic acid 67.3%; Oppler-Boas bacilli 64.4%; palpable tumor 63.4%.

Next to be considered are those diseases and entities which are associated with hyperchlorhydria. Ulcer is the only one to be considered in detail.



*Causes of Hyperacidity.*

### Peptic Ulcer

The fundamental cause remains Unknown in spite of the enormous amount of investigation. Many theories have been advanced, -vascular (Virchow); infectuous (Rosenow); neurogenic (Bergmann), but usually only three are considered now as having any importance. The three theories are: 1, psychogenic; 2, ductless glandular; 3, inflammatory.

1, Rothchild (74), after completing a psychoanalytic study of 32 consecutive patients, with ulcer, at Mount Sinai Hospital, found that they gave evidence of a profound neurosis, usually of a definite type. They were the aggressive, sadistic type and were chronically frustrated emotionally. These repressed emotions cause them to eat themselves up inwardly.

The tendency to ulcer has been termed ulcer diathesis. Droper stated that certain antropometric relations, as well as certain psychologic factors, are characteristic of ulcer bearing patients, and are called ulcer constitution.

Hurst and Stewart described hyperesthenic gastric diathesis and intimated inborn variation from the average normal, which manifests itself in short stomach accompanied by active peristalsis and rapid evacuation, and in hyperchlorhydria and gastric hypersecretion.

2, The ductless glandular factor seems to be predominant in males. In dogs during estrus the lesions healed

but during lactation the erosions enlarged and secretion was increased. This suggests relationship of anterior pituitary to secretion and peptic ulcer.

Histamine is present in gastric juice and the concentration it attains is directly proportional to the rate of secretion of gastric juice. The vagi during activity liberate histamine or histamine-like substance, which stimulates the parietal cells. Since histamine has a strong effect on the blood vessels, and is able to produce stasis in capillaries, which may lead to formation of erosion in the gastric mucosa, it is possible that histamine may be a cause of ulcer due to abnormal functioning of the gastric secretory mechanism (33).

3, The inflammatory theory includes a great many causative factors. Listed as elements predisposing to ulcer are: dietetic errors, alcohol, tobacco, focal and general infection.

Three important factors as the cause of ulcer, should be considered. a, Mechanical irritants or exogenous factor has often been ascribed importance in ulcer. That it is not very important is illustrated by the fact that Abyssinians are less prone to ulcers than are we, and they use large amounts of cayenne pepper.

b, That the acid factor is important is brought out by certain characteristics of the disease.

Ulcers occur only in regions of the gastro intestinal tract which are in contact with Hcl. They are found in the stomach, beginning duodenum, and jejunum when it is anastomosed to the stomach. May also find ulcer in Meckel's diverticulum or in esophagus if some aberrant tissue is present. The ulcers always commence in an acid media and gastric ulcer is usually found on the lesser curvature and pylorus, while the duodenal ulcer is always situated in the first part above the ampulla of Vater, the part, therefore, which is most acted upon by the unneutralized acid gastric juice.

Using histamine and neutral red food fractional test meal, the dictum "no free acid, no ulcer" can be confirmed. (75, 74, 73, 71).

c, Tissue resistance is influenced by mucin, vascularity and antiferments.

That vascularity is important is shown by experiments of Light, Bishop, and Nened (76). They injected pilocarpine hydrochloride into the lateral ventricles of rabbits, and found this caused the formation of gastric ulcer. They believed the ulcer was the result of the reduction of blood supply, to the area involved, due to brain impulse. It has been mentioned before that histamine may produce ulcer by action on the blood vessels.

Nechales and Coyne (77) showed that a normal person

injected with pilocarpine has an increase in secretion of visible mucus, while patients with ulcer do not show this increase in mucus secretion.

Pathology - The location of both duodenal and gastric ulcer has been discussed so we will pass to the appearance of the mucous membrane through the gastroscope.

The mucosa is dark and has a thick, heavy appearance as shown by the height of the folds. The ulcerating crater can sometimes be seen.

Formerly it was believed that ulcers always meant hyperacidity. We know now that about 50% of patients show high normal or hyperacid conditions. Occasionally subacidity occurs but rarely anacidity.

The acid content in duodenal ulcer is high more often than in gastric ulcer. Their clinical symptoms are the same as they have been considered under peptic ulcer.

Palmer (78) states that his studies of the clinical relationship of free Hcl to active ulcer indicate that in no instance in which the ulcer gave characteristic symptoms could there be an absence of Hcl.

Gastric analysis besides the atypical acid curve, shows an increase in total nitrogen and non-protein nitrogen positions of gastric juice. These are not nearly so marked as in carcinoma. The following chart shows the relationship in this respect between ulcer, carcinoma and the normal (72, 33).

	T.Nitrogen	Protein N	N.P.N.	Amino acid /V	Urea Nit.	Ammonia <sup>2</sup> Nitro
Average normal	48.18 mgm%	22.59	25.5	7.22	2.58	5.19
Gastric Ca.	82.54	54.59	59.77	20.31	9.48	13.67
Ulcer	65.24	32.58	31.09	7.72	4.17	5.54

Prognosis - The prognosis in most cases of ulcer is good. All evidence points to chronicity of the disease and that treatment is merely palliative. It is a disease which is prone to recur if great care is not taken by the patient to observe all rules laid down by his physician.

Forsyth had patients which suffered relapses from 1-7 times in from 1-12 years. In a survey of 1435 cases it is reported that 86% lived their expectancy of 59 years (73,79).

The best results are seen with medical care based on acid neutralization, and with a partial gastrectomy. Where achlorhydria is established there is no recurrence. Winkelstein (74) believes that harmless achlorhydria is beneficial. Gastric secretion is produced chiefly in two ways. The cephalic by way of the vagus and the chemical or hormonal phase by absorption of secretagogues, through the antrum. The cephalic phase in gastric secretion is high in duodenal ulcer, and low or normal in gastric ulcer. The chemical phase of the secretion is normal in duodenal ulcer and low in gastric ulcer.

Treatment - Medical treatment is the most satisfactory method if it proves to be sufficient.

It has been noted that partial gastrectomy produces true achlorhydria in most patients having gastric ulcer.

Winkelstein suggests subphrenic vagotomy and partial gastrectomy in patients having duodenal ulcer.



### Miscellaneous

Many pathological processes have been mentioned in literature, which cause a departure from the normal gastric curve. Few of them have been studied thoroughly by investigators, so a table from Bell (51) will be reproduced so as to give some idea as to the number and frequency of diseases causing acid secretory changes. The table also gives an impression of the frequency with which these various diseases occur.

Diseases	Number of Cases	Achlor-hydris	Hypo	L.N.	Norm.	H.N.	Hyper
Normal	100	4	1	10	59	18	8
Chronic gastritis	11	45.4	18.1	9	0	18.1	9
Gast.Ulcer	24	4.1	12.5	16.6	20.8	25	20.8
Ga. Stomach	10	30	30	20	10	10	0
Duod.Ulcer	34	0	0	11.7	8.8	26.4	53
Viscer-optosis	19	10.5	26.3	26.3	15.7	9	21
Gall Stones	7	14.2	0	0	57.1	14.2	14.2
Chronic Appendicitis	13	23	0	7.6	38.4	7.6	23.1
P.A.	6	100	0	0	0	0	0
Tabes Dorsalis	9	11.1	11.1	22.2	22.2	11.1	22.2
Disseminated Sclerosis	8	0	12.5	12.5	50	25	0
Rheumatoid Arthritis	8	37.5	12.5	12.5	0	0	37.5
Neurasthenia	20	10	30	5	25	5	25
Psychosthenia	11	9	18.1	9	45.4	18.1	0

### Significance of Gastric Acidity

The significance of gastric acidity, per se, is slight. The isolated fact that an individual has abnormal gastric secretion is of no diagnostic value. The mechanism concerned in producing acid is so intricate that each laboratory procedure must be carefully defined if the test is to be of value.

The difficulty of attaching significance to gastric acidity is further enhanced by the fact that normal physiological processes produce great changes in the acid content of the stomach. The variation of the apparently normal individual makes it difficult to ascertain the point at which normalcy ceases.

Gastric acidity is not to be considered as a means of making a diagnosis. It, along with the clinical history, however, can serve as a guide along which a train of thought which will enable one to make a positive diagnosis, can be established.

Some individuals with apparent anacidity are able to secrete acid with histamine. If free Hcl is present after histamine stimulation the actual level of the acidity is of little, if any, diagnostic value.

True anacidity is of diagnostic value. Sometimes the lack of acid is transient and is evidence that some, usually temporary, pathological process is going on.

The combination of low secretory volume with complete absence of acid is practically diagnostic of serious organic pathology involving the stomach.

Hypersecretion is probably not as significant an indicator of pathology as is acidity. When confronted with residual hypersecretion without food retention, think of early stage of ulcer formation. If there is residual hypersecretion with food retention, pyloric obstruction must be ruled out.

The abnormal functioning of the nervous system may also account for hyperacidity.

The examination of gastric juice should not be limited to the acid. A test should be made for occult blood and studies should be made on the total nitrogen and non-protein nitrogen partitions of gastric juice.

With a thorough clinical history and a complete study of the gastric juice one can attach a good bit of significance to the acid concentration present if the procedure was properly controlled.

### Conclusions

Gastric acidity plays an important role in every person's life. That the role it plays is destined, is true, because the amount of acid present is characteristic to each individual and the diseases to which that individual

is prone are in some way related to acid present.

Men have a higher concentration of acid than do women. They do not have the gradual fall to a certain level and there a plateau, that is characteristic of women.

That age shows a gradual decrease of the acidity is known. Perhaps this is a factor which makes certain diseases common in the later decades of life.

The acid in the gastric juice has a disinfecting action. This prevents the multiplication of the countless number of bacteria ingested. These bacteria in a stomach which lacks acid multiply and act upon the carbohydrates, splitting them into organic acids, such as, lactic, acetic, and butyric.

The lack of acid may impair the motor power so that the stomach cannot empty itself properly, but regurgitation into the esophagus may occur.

The proper hydrogen ion concentration must be maintained if digestion is to proceed at an optimum. Pepsin cannot act in an alkaline media. It is also true that anacidity, in some way, distorts the power of absorption of the stomach and a macrocytic anemia may result.

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